

Award Number: W81XWH-12-1-0170

TITLE: Prospective Evaluation of Intraprostatic Inflammation and Focal Atrophy as a Predictor of Risk of High-Grade Prostate Cancer and Recurrence after Prostatectomy

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REPORT DATE: September 2016

TYPE OF REPORT: Final Report

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
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REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.					
1. REPORT DATE September 2016		2. REPORT TYPE Final		3. DATES COVERED 1Jul2012 - 30Jun2016	
4. TITLE AND SUBTITLE Prospective Evaluation of Intraprostatic Inflammation and Focal Atrophy as a Predictor of Risk of High-Grade Prostate Cancer and Recurrence after Prostatectomy				5a. CONTRACT NUMBER W81XWH-12-1-0170	
				5b. GRANT NUMBER PC110754	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Elizabeth A. Platz on behalf of the study team E-Mail: eplatz1@jhu.edu				5d. PROJECT NUMBER W91ZSQ1295N667	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Johns Hopkins University 615 N. Wolfe St. Baltimore, MD 21205				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT We evaluated, in 2 nested case-control studies, intraprostatic inflammation and focal atrophy as tissue markers for risk of future diagnosis of prostate cancer and for prognosis. For incidence, we found in the placebo arm that 76% of cases and 69% of controls had 1+ biopsy core (of 3 assessed) with inflammation, most of which was chronic. The OR of lower-grade prostate cancer tended to increase with number of biopsy cores with inflammation (compared with 0 cores with inflammation, some cores OR=1.96, all cores OR=2.94, P-trend=0.1). In the finasteride arm, prevalence of inflammation did not differ between cases (76%) and controls (75%). For focal atrophy, we observed a possible positive association in the placebo arm, but an inverse association in the finasteride arm; we could not rule out treatment effect on the appearance of atrophy in the latter. For prognosis, the OR of recurrence comparing top and bottom quartiles of minimum mast cell density was 0.58 (95% CI 0.40-0.86; P-trend=0.004) taking into account matching factors age, race, Gleason sum, and pathologic stage. We conclude that intraprostatic inflammation pre-dating prostate cancer diagnosis and recurrence may influence risk and prognosis.					
15. SUBJECT TERMS Nothing listed					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT UU	18. NUMBER OF PAGES 10	19a. NAME OF RESPONSIBLE PERSON USAMRMC
a. REPORT U	b. ABSTRACT U	c. THIS PAGE U			19b. TELEPHONE NUMBER (include area code)

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1. INTRODUCTION:

With respect to healthy men, at this time, we do not know how to prevent the development of prostate cancer that has the potential to be aggressive, nor do we have a tool to identify men who would most benefit from preventive interventions for aggressive disease. With respect to men with early prostate cancer, at this point, we still cannot predict with certainty which men are more likely to suffer and die of their prostate cancer after prostatectomy. In this population-based research project, we directly addressed these major problems. We evaluated, in two nested case-control studies, intraprostatic inflammation and focal atrophy, a prostate lesion that is often inflamed, as tissue markers for risk of future diagnosis of prostate cancer, and for prognosis at the time of surgery for clinically localized prostate cancer. Our overall hypotheses were: 1) Chronic intraprostatic inflammation is a cause of prostate cancer that is more likely to be aggressive and recur. 2) Focal atrophy, a prostate lesion that is often inflamed, is a risk and prognostic indicator. Our findings for incidence (future diagnosis) were supportive of this hypothesis. Our findings for prognosis were more nuanced: mast cells (a type of tissue resident immune cell) within the tumor at the time of prostatectomy appeared to protect against future recurrence, while mast cells in apparently benign regions appeared to increase the risk of recurrence.

2. KEYWORDS:

Prostate cancer, risk, incidence, recurrence, inflammation, focal atrophy, mast cells, immune cells, tissue microarray, biopsy, image analysis, odds ratio.

3. OVERALL PROJECT SUMMARY:

Prostate cancer incidence: For Aims 1 and 2, we completed **Tasks 1, 2, 3a-c, 4a-b, f** in Years 1 and 2. In Year 3, we on-boarded the new biostatistician mentioned in the last progress report (arrived in 8/2014) and trained him for these analyses (and those in Aims 3 and 4), we cleaned the merged pathology-PCPT-SELECT data from the review of the H&E stained slide images (**Task 7a**), and performed the statistical analysis of the merged data to address the association of inflammation (Aim 1) and focal atrophy (Aim 2) with prostate cancer risk (**Task 7b**), and began to draft the manuscript for inflammation and risk (**Task 7d**). We presented the findings in talks and small prostate-cancer meetings for initial feedback (**Task 7c**). In Year 4, we finalized the statistical analyses for inflammation and atrophy, and completed the draft of the inflammation manuscript, the final version for which is under SWOG co-author review (expected submission in September 2016). We remain unsure of the explanation for the focal atrophy results (possible positive association in those who were previously in the PCPT placebo arm, but possible inverse association in those who were previously in the PCPT finasteride arm) because we cannot at this time determine whether the focal “atrophy” we observed in the finasteride arm is the same lesion that we observed in the placebo arm or a different lesion induced by the drug (see KEY RESEARCH ACCOMPLISHMENTS below for discussion). In Years 3 and 4, we began and completed IHC staining of 1,460 slides for the immune cell markers (CD4, CD8, CD68, CD20, FOXP3) for the 292 men in the linked PCPT-SELECT set (**Task 3e,f**). Work remaining includes scoring these slides, and performing data cleaning and the statistical analysis. The team is committed to completing this work.

Prostate cancer recurrence: For Aims 3 and 4, we completed **Tasks 1, Task 5a-c, Task 5 d-e** (for mast cells), we optimized and implemented a more efficient method of image analysis for IHC-stained TMA sections and documented its accuracy relative to manual counting for mast cells and optimized double stains for CK8 and CD4, CD8, CD20, CD68, and FoxP3 (**Relevant to Task 3f and Task 5e**) in Years 1 and 2. In Year 3, we completed image analysis for mast cell numbers and total epithelial area with the PIP software (**Task 6c** for mast cells), merged the data with the Brady recurrence database and cleaned the merged data (**Task 8a** for mast cells) and performed the statistical analysis (**Task 8b** for mast cells), presented some of the results at a national meeting (Hempel HA et al. AACR 2015, Philadelphia, PA); **Task 8c** for mast cells), and began drafting a manuscript (**Task 8d** for mast cells). In Year 4, we performed additional statistical analyses, completed the manuscript, and have submitted it for publication. Because we observed differential associations of mast cells with recurrence based on whether the mast cells were intratumoral (inverse association) or within apparently benign tissue (positive association), we lowered the priority of the review of the H&E stained images for overall inflammation (percent tissue area involved) for the recurrence set (assessment of bulk inflammatory cells may not be informative) and instead, have prioritized the remaining immune cell markers (**Tasks 5c,d, 6c,d, 8a,b**). Over the course of the 4 years of this grant, we continued to improve and enhance our methods of immune cell

detection. We will not stain these sections until we are satisfied that we have our multiplex immunofluorescence method. We also have held off assessing focal atrophy in the recurrence TMA set (**Task 6b,d**) based on the current inability to currently distinguish focal atrophy from possible treatment effect of finasteride (see KEY RESEARCH ACCOMPLISHMENTS below for discussion). The team is committed to completing this work.

KEY RESEARCH ACCOMPLISHMENTS:

Prostate cancer incidence: The final data included 96 prostate cancer cases and 194 controls frequency matched on age and race. Of the cases, Gleason sum was known for 81%; only 9 had Gleason sum $\geq 4+3$.

Chief results from Aim 1: Among men previously randomized to the PCPT placebo arm, prostate cancer cases and frequency-matched controls did not significantly differ in their characteristics except for family history of prostate cancer and possibly for measures of adiposity. Demographic, anthropometric, and dietary characteristics of controls were generally not strongly associated with extent of inflammation. In those previously in the PCPT placebo arm, we observed that 76.3% of cases (81.4% of lower-grade) and 68.9% of controls had at least one baseline biopsy core with inflammation. This percentage was modestly lower than what we previously reported in a different group of controls sampled from the PCPT (78%; (1)). Of controls who had at least one biopsy core with inflammation, on average, 4.5% of the benign tissue area for each of these controls had inflammation. Most of the inflammatory cells present reflected chronic inflammation (e.g., mononuclear cells that were morphologically recognizable as lymphocytes and macrophages). Grade 3 chronic inflammation was not common (5.8% of controls had at least one core) and grade 3 acute inflammation was very uncommon (1.2% of controls had at least one core). While not statistically significant, having at least one biopsy core with inflammation was possibly positively associated with risk of prostate cancer (OR=1.51, 95% CI 0.65-3.50), especially lower-grade disease (OR=2.07, 95% CI 0.76-5.59), adjusting for the matching factors age and race (Table 1). In men with PSA <2 ng/mL at baseline, associations for total (OR=2.65, 95% CI 0.83-8.42) and lower-grade (OR=2.08, 95% CI 0.64-6.75) prostate cancer were similar to overall. Further, risk of total and lower-grade prostate cancer tended to increase across none, some, or all biopsy cores with inflammation. These results were similar after additional adjustment for potentially confounding factors. Also, these results were nearly unchanged after adjusting for randomization to the SELECT treatment arms any inflammation: total OR=1.51, 95% CI 0.65-3.50; lower-grade OR=2.07, 95% CI 0.76-5.62).

Table 1. Association* between inflammation and prostate cancer, case-control study nested in linked PCPT-SELECT cohort

	Placebo arm		Finasteride arm	
	Total**	Lower grade	Total**	Lower grade
No. cases	43	33	53	36
At least one biopsy core with inflammation				
OR	1.51	2.07	1.04	1.01
95% CI	0.65-3.50	0.76-5.59	0.48-2.23	0.42-2.42
Extent of biopsy cores with inflammation				
None				
OR	1.00	1.00	1.00	1.00
95% CI	Reference	Reference	Reference	Reference
Some				
OR	1.47	1.96	1.00	0.95
95% CI	0.63-3.47	0.71-5.41	0.46-2.18	0.39-2.32
All				
OR	1.83	2.94	1.39	1.58
95% CI	0.41-8.15	0.61-14.27	0.37-5.19	0.37-6.73
P-trend	0.3	0.1	0.7	0.7

*Adjusted for age and race; **Cases and controls (86 in placebo, 108 in finasteride arm) were frequency matched on age and race. Lower-grade cases were Gleason <4+3 and higher-grade cases were Gleason $\geq 4+3$. 5 cases had missing Gleason; ***Final PSA reported in SELECT (controls) or closest to diagnosis (cases)

In those previously assigned to the PCPT finasteride arm, prostate cancer cases and frequency-matched controls did not significantly differ in their characteristics except for family history of prostate cancer and daily intake of energy, macronutrients, and possibly red meat. In contrast to the placebo arm, in the finasteride arm, several demographic, anthropometric, and dietary characteristics of the controls appeared to be associated with extent of inflammation. Controls previously in the PCPT finasteride arm appeared to have a slightly higher prevalence (74.8% vs 68.9%), but not extent of inflammation, than controls previously in the placebo arm. Like in the placebo arm, most inflammation was chronic. Grade 3 chronic inflammation was not common (6.5% of controls had at least one core), and none had grade 3 acute inflammation. However, lower-grade cases in the finasteride arm appeared to have a slightly lower prevalence (75.1% vs. 81.4%) and extent of inflammation than lower-grade cases in the placebo arm. Unlike in the placebo arm, among those previously in the PCPT finasteride arm any inflammation was not associated with risk of total or lower-grade prostate cancer, although we could not rule out a modest positive association among men who had all biopsy cores with inflammation (Table 1), or in men with PSA <2 ng/mL at baseline (any inflammation - total: OR=1.39, 95% CI 0.55-3.56; lower-grade: OR=1.88, 95% CI 0.59-5.98). Results were unchanged after further adjusting for potentially confounding factors. While the patterns of association between any inflammation and total (P-interaction=0.5) and lower-grade (P-interaction=0.3) prostate cancer appeared to be different in the two PCPT treatment arms, we did not detect statistically significant interaction.

Chief results from Aim 2:

In the men previously randomized to the placebo arm, we noted a possible positive association between focal atrophy and prostate cancer overall (OR=1.53) and lower-grade disease (OR=1.74) taking into account the matching factors age, race, and family history. However, neither of these results was statistically significant and no trend was apparent across extent (none, some, all biopsy cores with focal atrophy). In contrast, among men previously randomized to the PCPT finasteride arm, we observed a possible inverse association for prostate cancer overall (OR=0.42) and lower-grade disease (OR=0.38), albeit the associations were not statistically significant. We also observed that the OR of prostate cancer overall decreased with increasing extent of focal atrophy (compared with none, some OR=0.47, all OR=0.15, 95% CI 0.03-0.79, P-trend=0.02). While a blinded study indicated that finasteride did not notably affect the extent of atrophy in prostate biopsies in the men who participated in a BPH treatment trial (2), in our hands, we suspect that some of the “atrophy” we recorded is an artifact of finasteride treatment. And, that artifact could account for the inverse association with prostate cancer that we observed as follows: Men who were maximally compliant with taking finasteride and/or responsive to the drug’s inhibition of the 5 α reductase would have experienced greater extent of “atrophy”, and men who were maximally compliant with taking the drug and/or or responsive to the drug’s inhibition of the 5 α reductase would have been less likely to have diagnosed with prostate cancer (i.e., the findings of PCPT(3)).

Prostate cancer recurrence: Final data included 462 men who recurred (cases) and 462 men matched to the cases who did not recur (controls) from the Brady nested case-control study of recurrence. As indicated in OVERALL PROJECT SUMMARY, we have held off assessing focal atrophy in the recurrence TMA set based on the current inability to currently distinguish focal atrophy from possible treatment effect of finasteride

Chief results from Aim 3:

Here we report on the exciting finding for mast cells, a component of the innate immune system. We quantified mast cells and epithelial area in the TMA spots by PIP digital image analysis (the method integrates whole slide imaging, virtual microscopy, and ImageJ based analysis algorithms). We documented that the counts for IHC-positive cells are comparable to manual assessment for mast cells. We defined minimum mast cell density as the number of mast cells per total TMA spot area among each man’s cancer or benign TMA spots. Mast cell density was significantly higher in tumor than in benign areas (P<0.0001). In controls, higher mast cell density in tumor (Q4 vs Q1: OR=0.40, P-trend<0.01), but not benign tissue (p-trend=0.1), was inversely associated with higher-grade disease (Gleason score 4+3 or higher). Minimum mast cell density was higher in cases and controls in both tumor (P=0.0005) and in benign tissue (P=0.02). The OR of recurrence comparing top and bottom quartiles of minimum mast cell density was 0.58 (95% CI 0.40-0.86; P-trend=0.004) taking into account matching factors age, race, Gleason sum, and pathologic stage (Table 2). The patterns of this association were similar when using the mast cell number and ratio of mast cell number to epithelial or

stromal area (Table 2). In contrast, higher mast cell density per tissue area in normal appearing tissue from these men with prostate cancer was positively associated with risk of recurrence (OR=1.48, 95% CI 1.02-2.14, P-trend=0.007; Table 2). In addition to this DOD grant, this work was supported by Prostate Cancer Biorepository Network (PCBN) (Department of Defense Award No W81XWH-10-2-0056 and W81XWH-10-2-0046), which manages and distributes these recurrence TMAs, Department of Defense PCRP Award No W81XWH-14-1-0364 (to Dr. Karen Sfanos), NIH/NCI prostate SPORE pathology core (Award No 5P50CA058236), which provided additional infrastructure and pathology support.

Table 2. Association between quartiles of minimum* mast cells parameters in tumor or benign tissue and risk of prostate cancer recurrence, Brady Recurrence Nested Case-Control Study.

Quartile** minimum mast cell parameter	OR of prostate cancer recurrence							
	Tumor tissue				Benign tissue			
	No. of recurrence cases/controls	OR	95% CI	P	No. of recurrence cases/controls	OR	95% CI	P
Mast cell count								
1 (lowest)	154/126	1.00	Reference		96/121	1.00	Reference	
2	134/118	0.87	(0.61-1.23)		89/120	0.96	(0.66-1.40)	
3	77/109	0.53	(0.36-0.80)		115/114	1.27	(0.88-1.83)	
4 (highest)	97/109	0.66	(0.44-0.98)		165/110	2.07	(1.41-3.05)	
	P-trend			0.02				<0.001
Mast cell Density								
1 (lowest)	150/116	1.00	Reference		98/114	1.00	Reference	
2	126/115	0.81	(0.57-1.16)		84/117	0.81	(0.55-1.19)	
3	94/117	0.60	(0.41-0.87)		140/120	1.36	(0.95-1.93)	
4 (highest)	92/114	0.58	(0.40-0.86)		143/114	1.48	(1.02-2.14)	
	P-trend			0.004				0.007
Ratio of mast cells to epithelial area								
1 (lowest)	152/116	1.00	Reference		88/117	1.00	Reference	
2	104/114	0.67	(0.46-0.97)		109/115	1.27	(0.87-1.85)	
3	110/117	0.68	(0.47-0.99)		116/114	1.41	(0.96-2.08)	
4 (highest)	96/115	0.60	(0.41-0.88)		152/119	1.79	(1.22-2.64)	
	P-trend			0.03				0.004
Ratio of mast cells to stroma								
1 (lowest)	150/116	1.00	Reference		104/117	1.00	Reference	
2	126/115	0.81	(0.57-1.16)		97/113	0.96	(0.66-1.41)	
3	94/117	0.60	(0.41-0.87)		126/117	1.20	(0.84-1.71)	
4 (highest)	92/114	0.58	(0.40-0.86)		138/118	1.32	(0.92-1.91)	
	P-trend			0.01				0.07

5. CONCLUSION:

Aim 1: This first prospective study of men without indication for biopsy provides some evidence, albeit not statistically significant, in support of the hypothesis that inflammation influences the development of prostate cancer. Interestingly, the magnitude of the association between inflammation in baseline biopsies and lower-grade disease that we observed is similar in magnitude to what we observed previously (Gleason <7, at least one 1 core with inflammation: OR=1.57, 95% CI 0.83-3.00 (1) in a different set of men from the PCPT in whom we assessed inflammation in the same biopsies that were used to rule in or the presence of cancer. In that

prior study, we noted a stronger association for higher-grade disease (Gleason ≥ 7 ; OR=2.24, 95% CI 1.06–4.71; across none, some, all cores with inflammation: P-trend=0.01). In the linked PCPT-SELECT study, we could not rule in or out an association with higher-grade disease because the number of higher-grade cases was too small to evaluate. Taken together, our current findings from PCPT-SELECT in which we assessed inflammation in tissue removed by biopsy in months to years before the diagnosis of prostate cancer, and PCPT in which we assessed inflammation in the same prostate biopsy tissue used to rule in or out the diagnosis of prostate cancer (1) support an etiologic role of intraprostatic inflammation in the development of prostate cancer. One potential pitfall of this linked PCPT-SELECT study is that, in general, when chronic inflammatory conditions increase the risk of cancer (e.g., gastritis-associated stomach cancer, colitis-associated gastric cancer, and hepatitis-associated liver cancer), its effect generally is assumed to take substantial time, often decades. Thus, while we assessed intraprostatic inflammation before the diagnosis of prostate cancer, the time interval between them was relatively short (mean: 5.9 years; range: 1.2-10.5 years) especially for prostate cancer, which is generally slow growing. It is thus unclear whether we assessed inflammation in the etiologically relevant window, whether the inflammation we assessed is correlated with the inflammation that may be etiologically relevant, or perhaps most importantly, whether enough time lapsed between the finding of the presence of inflammation and the development of cancer.

With respect to our second hypothesis, inflammation was not related to prostate cancer risk in men treated with finasteride, as consistent with our prior study in the PCPT (4), despite the fact that in the current study the men were no longer taking finasteride during SELECT after having taken it for 7 years during PCPT. While the biological basis for this lack of association is not known, we speculated previously (4), including that finasteride-associated intraprostatic inflammation may not be pro-carcinogenic or may not be present sufficiently long (use was for 7 years) to result in cancer development.

Aim 2: The findings in the placebo arm are supportive of the hypothesis that focal atrophy detected in prostate tissue assessed before the diagnosis of prostate cancer is associated with increased prostate cancer risk. We could not rule out treatment artifact in the call of “atrophy” in finasteride arm.

Aim 3: Our results suggest that a intratumoral mast cells may be protective against prostate cancer recurrence following treatment by radical prostatectomy for clinically localized disease, even after taking into account the currently use clinicopathologic prognostic factors, and thus, could potentially serve as a prognostic biomarker after prostatectomy. We noted that the inverse association was present when standardizing the number of mast cells by the tissue area reviewed, but also was present when considering the raw count as well as the count per epithelial or stromal area. Given that we reviewed up to 4 cancer TMA spots per man, we considered several expressions of the typical density across a man’s TMA spots: the most consistent findings were observed when using the minimum, rather than the mean, maximum, or standard deviation of mast cell density among each man’s TMA spots assessed. We do not know why the mast cell minimum of each man’s TMA spots was the most robustly different measure between recurrence cases and controls. We do know that mast cell numbers within different regions of the tumor can vary depending on a number of factors including the presence of other inflammatory cells and/or immune stimuli, local cytokine production. Thus, if intratumoral mast cells indeed do protect against recurrence, we speculate that the region with the lowest number (rather than the average number, the maximum number, or the variability in number across regions of the tumor) may provide the most information about risk of recurrence.

In contrast to our finding in tumor, we observed that mast cells in benign tissue were positively associated with recurrence. This finding is consistent with our hypothesis that mast cells would be positively, rather than inversely associated with risk of recurrence because they release TNF- α , which can recruit macrophages to the site of inflammation and contribute to T cell-mediated chronic inflammation. Many other biological explanations are also possible given that mast cells also influence angiogenesis and metastasis. We should note that in the construction of these TMAs (done previously), we sampled benign areas that were not overtly inflamed.

Aim 4: No results from which to draw conclusions.

In summary, our work supports that intraprostatic inflammation pre-dating prostate cancer diagnosis and recurrence may influence risk (in men not taking finasteride) and prognosis.

6. PUBLICATIONS, ABSTRACTS, AND PRESENTATIONS:

Publications:

None to date. Aim 1 primary manuscript on inflammation and prostate cancer risk is with the SWOG (PCPT, SELECT) investigators for their review. We expect to submit the manuscript in September 2016. Aim 3 manuscript on mast cells and recurrence was submitted for publication (to *Cancer Immunology Research*).

Presentations and abstracts:

Talks in which data from Aim 1 were presented:

“Inflammation and prostate cancer”. Joint Meeting of the Johns Hopkins Prostate Cancer SPORE and the Thomas Jefferson/University of Pennsylvania Prostate Cancer SPORE. November 7, 2014, Philadelphia, PA.

“Updates on the epidemiology of prostate cancer and BPH/LUTS”. Prostate Research Day, Johns Hopkins University (attendees include Prostate Cancer Advisory Board members and SPORE External Advisors [e.g., including Peter Gann, Howard Soule, Eric Klein, Howard Scher], as well as JH researchers), February 21, 2015.

“Successes in working together to identify modifiable risk factors and tissue-based markers: prostate cancer risk and recurrence”. Ohio State University James Cancer Center, December 10, 2014, and Department of Hygiene and Epidemiology, University of Ioannina, Ioannina, Greece, July 7, 2015.

Poster in which data from Aim 3 were presented:

Abstract 2342: Characterization of inflammatory markers and mast cells in association with prostate cancer. Heidi Hempel, Ibrahim Kulac, Nathan S. Cuka, Toby C. Cornish, Elizabeth A. Platz, Angelo M. DeMarzo, Karen S. Sfanos. American Association for Cancer Research Annual Meeting, April 20, 2015, Philadelphia, PA.

7. INVENTIONS, PATENTS AND LICENSES:

None

8. REPORTABLE OUTCOMES:

Through this work, we developed a resource for prostate cancer researchers: a new cohort derived from the linkage of the PCPT and SELECT trials. This cohort consists of men who were negative for prostate cancer on PCPT end-of-study biopsy and who then enrolled in SELECT. Linking these 2 cohorts is the ONLY epidemiologically sound approach for prospectively testing the association of tissue markers in men without an indication for biopsy or surgery with prostate cancer incidence – at this time and in the foreseeable future. Access to this linked resource is via SWOG (<http://swog.org/Visitors/Biorepository/>).

The recurrence TMAs that we used were previously developed by Drs. Platz and De Marzo based on a nested case-control study they developed under DOD funding. These TMAs are available through the DOD-supported PCBN (<http://www.prostatebiorepository.org/>).

9. OTHER ACHIEVEMENTS:

The mast cell research in Aim 3 was led by Heidi A. Hempel, a doctoral candidate at the Johns Hopkins School of Medicine; this work on mast cells and recurrence forms a component of dissertation. Her advisor is Karen Sfanos, Assistant Professor at the Johns Hopkins School of Medicine, a collaborator of Drs. Platz and De Marzo on the basic science of infectious agents and resultant inflammation in the etiology of prostate cancer.

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APPENDICES:

None

SUPPORTING DATA:

None